UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,012,140 B1
APPLICATION NO. : 10/619362
DATED : March 14, 2006
INVENTOR(S) : A. Dean Sherry, Mark Woods and Zoltan Kovacs

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 4, lines 14-17 should appear as follows:

FIGURE 3A and FIGURE 3B illustrates exemplary ^{1}H NMR spectra of ~~[Eu(S-RRRR-NO$_2$BnDOMA)]~~ [Eu(S-RRRR-NO$_2$BnDOTMA)] and [Eu(S-SSSS-NO$_2$BnDOTMA)], respectively, produced according to the present; and

Column 5, lines 60-67 through and including Column 6, lines 1-3 should appear as follows:

For example, when the three or more pendant arm carbon atoms C' have Δ orientations and the chirality of the one or more R^6-substituted ring carbons is selected such that the macrocyclic ring has an identical (δδδδ) orientation, then the tetraazacyclododecane ligand has a capped twisted square antiprism configuration. Or, when the three or more pendant arm carbon atoms C' have Λ orientations ~~and~~ and the chirality of the one or more ring carbons is selected such that the macrocyclic ring has a (λλλλ) orientation, then the tetraazacyclododecane ligand again has a capped twisted square antiprism configuration.

Column 8, lines 61-67 through Column 9, lines 1-11 should appear as follows:

In certain preferred embodiments of the method 100, the contrast agent further includes a carrier component, conjugated to one or more of the functionalized substituents R^6, as discussed above. In certain embodiments of the present invention, the CA includes at least one and up to twenty of the tetraazacyclododecane ligands. Such ligands may be covalently or noncovalently bonded to a carrier component, such as described above, comprising a portion of the contrast agent. Collecting several such ligands, and associated metal ions and bound water molecules, allows a larger effective magnetic resonance signal to be achieved at lower concentrations of contrast agent. In certain such embodiments, where the water molecule (H_2O) associated with the tetraazacyclododecane ligand has a τ_M^{298}, of between about 10 and about 100 nanoseconds, the water molecule associated with a contrast agent that further includes a carrier component has a ~~relativity~~ relaxivity at 298°C, r_1^{298}, of at least about 50 $mM^{-1} s^{-1}$.

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Column 11, lines 59-67 through Column 12, lines 1-5 should appear as follows:

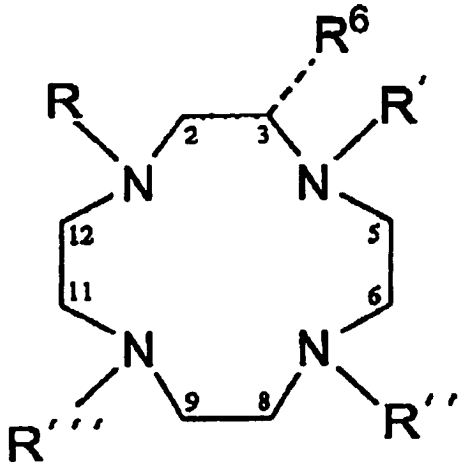
The two complexes [Gd(S-RRR- NO_2BnDOTMA)]$^-$ and ~~[Gd(s-ssss-N)$_2$BaDOTMA)]$^-$~~ [Gd(S-SSSS-NO_2BnDOTMA)]$^-$ have substantially different $1/T_2$ - temperature profiles, indicating substantially different water exchange ~~rates. The profile for [Gd(S-RRRR~~-N)$_2$BnDOTMA)]$^-$ [Gd(S-RRRR- NO_2BnDOTMA)]$^-$, rises, maximizes and then falls away with increasing temperature, indicative of fairly slow water exchange. In contrast, the profile for [Gd(S-SSSS-NO_2BnDOTMA)], did not reach a maximum within the temperature range study, indicative of a more rapid water exchange. The values of τ_M^{298} obtained by fitting procedures, well known to those skilled in the art, to profiles such as depicted in FIGURE 4, are summarized in TABLE 2. Also shown in TABLE 2 are the relaxivities of water molecules associated with these ~~somers~~ isomers at 25 and 37 °C.

Claim 1 should appear as follows:

The following clerical or typographical error was noted in Claim 1:

1. A magnetic resonance contrast agent compound comprising:

a ~~tetraacyclododecane~~ tetraazacyclododecane ligand having a general structural formula as follows:



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(claim 1 continued)

and comprising a ~~macrocylic~~ macrocyclic ring and wherein pendant arms R, R', R'' and R''' attached to a ring nitrogen have the general formula: -C'HR^{1}R^2 and for three or more of said pendant arms a chirality of said carbon atoms C' are identical for each of said three or more pendant arms, said R^1 are groups larger than hydrogen, and said R^2 is selected from the ~~goup~~ group consisting of:

an alcohol (-CH_2OH);

amides (-$CONR^3R^4$, where R^3 and R^4 are organic groups);

a carboxylate (-COOH);

phosphinates (-PO_2HR^5, where R^5 is an organic group); and

a phosphonate (-$PO(OH)_2$); and

wherein one or more of substituents R^6 is a group larger than a methyl group and is located on one or more ring carbons; and

a ~~paramagetic~~ paramagnetic metal ion coordinated to said tetraazacyclododecane ligand.

The correction to claim 1 is fully supported in Column 12, lines 48, 61 and 67 and Column 13, line 11.

Claim 5 should appear as follows:

5. The magnetic resonance contrast agent compound as recited in Claim 1, wherein said chirality of said carbon atoms C' is controlled to provide said three or more of said pendant arms with a Δ or Λ orientation, and wherein a chirality of a ring carbon bonded to said one or more of substituents R^6 provides said ~~macrocylic~~ macrocyclic ring with an opposite orientation, λλλλ or δδδδ, respectively, said tetraazacyclododecane ligand thereby having a monocapped square antiprism coordination geometry.

The correction to claim 5 is fully supported in Column 13, line 41.

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It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Claim 6 should appear as follows:

6. The magnetic resonance contrast agent compound as recited in Claim 5, wherein said R^2 group is said ~~alcohol~~ alcohol or amide, and further including a water molecule associated with said tetraazacyclododecane ligand and said ~~pararnagnetic~~ paramagnetic metal ion, said water molecule having a residence lifetime at about 298°K, τ_M^{298}, of ~~berween~~ between about 10 and about 5000 microseconds.

The correction to claim 6 is fully supported in Column 14, line 2, 4, 5 and 6.

Claim 7 should appear as follows:

7. The magnetic resonance contrast agent compound as recited in Claim 5, wherein said R^2 group is said carboxyl, and further including a water molecule associated with said ~~tetrcyclododecane~~ tetraazacyclododecane ligand and said paramagnetic metal ion, said water molecule having a residence lifetime at about 298°K, τ_M^{298}, of between about 100 and about 500 nanoseconds.

The correction to claim 7 is fully supported in Column 14, line 11.

Claim 8 should appear as follows:

8. The magnetic resonance contrast agent compound as recited in Claim 5, wherein said R^2 group is said phosphonate or said phosphinate, and further including a water molecule associated with said ~~tet azacyclododecane~~ tetraazacyclododecane ligand and said paramagnetic metal ion, said water molecule having a residence ~~lifetine~~ lifetime at about 298°K, τ_M^{298}, of between about 10 and about 100 nanoseconds.

The correction to claim 8 is fully supported in Column 14, lines 18 and 20.

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Claim 9 should appear as follows:

9. The magnetic resonance contrast agent compound as recited in Claim 1, wherein said R^1 is a methyl group, said R^2 is said ~~carboxyl~~ carboxyl, and said R^6 is a para-aminobenzyl group and said paramagnetic metal ion is Gd^{3+}.

The correction to claim 9 is fully supported in Column 14, line 24.

Claim 11 should appear as follows:

11. The magnetic resonance contrast agent ~~compund~~ compound as recited in Claim 1, wherein at least one of said one or more of substituents R^6 include a functional group selected from the group consisting of:

amino groups;

carboxylates;

isothiocyanates; and

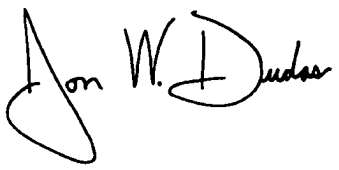
maleiimdes; and

a carrier component conjugated to said functional group.

The correction to claim 11 is fully supported in Column 14, line 31.

Signed and Sealed this

Twelfth Day of February, 2008



JON W. DUDAS
Director of the United States Patent and Trademark Office